Hospital acquired pneumonia

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Definition

Hospital acquired pneumonia (HAP) is defined as pneumonia that occurs 48 hours or longer after hospital admission and excludes any infection that is incubating at the time of admission[1]. It is also commonly termed nosocomial pneumonia. Ventilator-associated pneumonia is widely recognised as pneumonia developing after at least 48 hours of mechanical ventilation (MV), and can be considered a subgroup of HAP with distinct differences in terms of pathogenesis, histology, aetiology and prognosis. The concept of 'early-' and 'late-onset' HAP is also useful:

- *Early-onset HAP* is commonly defined as occurring within four days of hospitalisation, with *Streptococcus pneumoniae, Haemophilus influenzae and Staphylococcus aureus* the most frequently isolated organisms[2,3].
- *Late-onset HAP,* occurring five or more days after hospitalisation, is caused by pathogens such as enteric Gram-negative bacilli that have replaced the 'community' pathogens in the oropharynx.

Patients readmitted to hospital with pneumonia following recent hospital discharge may have features more consistent with HAP than with community acquired pneumonia (CAP).

Incidence and mortality

HAP is the third commonest nosocomial infection after urinary tract and surgical wound infection and carries the highest mortality[4]. The incidence of HAP varies with:

- *age:* less than five episodes per 1,000 discharges in patients younger than 35 years, increasing to 15 per 1,000 patients in the elderly
- *type of hospital:* lower in district hospitals than in large teaching hospitals, possibly related to differing complexity of patients' illnesses
- *type of ward:* uncommon in obstetric and paediatric wards, and most common in intensive care units (ICUs). Within ICUs, the incidence increases with rates of MV; for patients on MV, the incidence increases with length of stay in the ICU (rates of >35 episodes per 1,000 patient-days have been reported)[5].

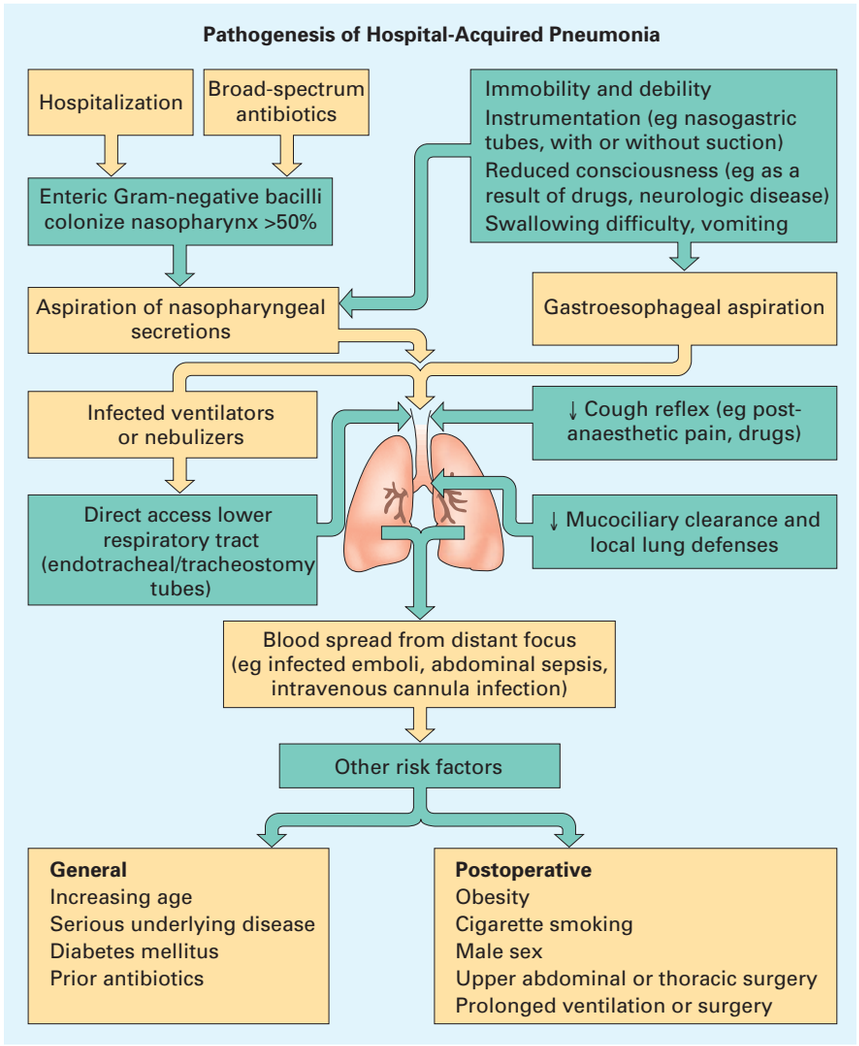

Fig 1. Pathogenesis of hospital acquired pneumonia (reproduced from Ref 6 by kind permission of The Medicine Publishing Company).

HAP has been estimated to add 5–9 days to the hospital stay of survivors, and the crude mortality rate may be as high as 70%[4]. Many of these deaths in patients with complex medical problems are not directly or solely related to infection. Attributable mortality has accordingly been estimated as one-third to one-half of all HAP deaths[1].

Pathogenesis

Factors associated with the pathogenesis of HAP are summarised in Fig 1[6]. Aspiration of bacteria that colonise the

upper respiratory tract is the main route of infection. Although aspiration is common in healthy people during sleep (46%)[7], factors that promote aspiration, such as impaired level of consciousness, supine position and placement of a naso-gastric or endotracheal tube, increase the risk of HAP.

Colonisation of the oropharynx by enteric Gram-negative bacilli increases with increasing severity of underlying illness and occurs in up to three-quarters of critically ill patients within a few days of admission[8]. Potential reservoirs for oropharyngeal colonisation include the stomach, sinuses, nasal mucosa and dental plaque[9]. Disruption of these environments, for example, concurrent sinusitis or raising the gastric pH and allowing gastric colonisation, increases the risk of HAP. Antibiotic treatment is one of the main mechanisms related to oropharyngeal colonisation.

Changes in respiratory epithelial cells that favour bacterial adherence (loss of surface fibronectin, alteration of cell surface carbohydrates or of epithelial cell bacterial receptors) are also important and may be influenced by nutritional status[10].

A less common mechanism of infection is direct inoculation of bacteria into the lower respiratory tract, for example, inhalation of aerosolised pathogens from contaminated respiratory equipment (nebulisers) or from the environment, for instance from showers and water systems colonised with Legionella. Haematogenous spread occurs occasionally from a distant site to the lungs.

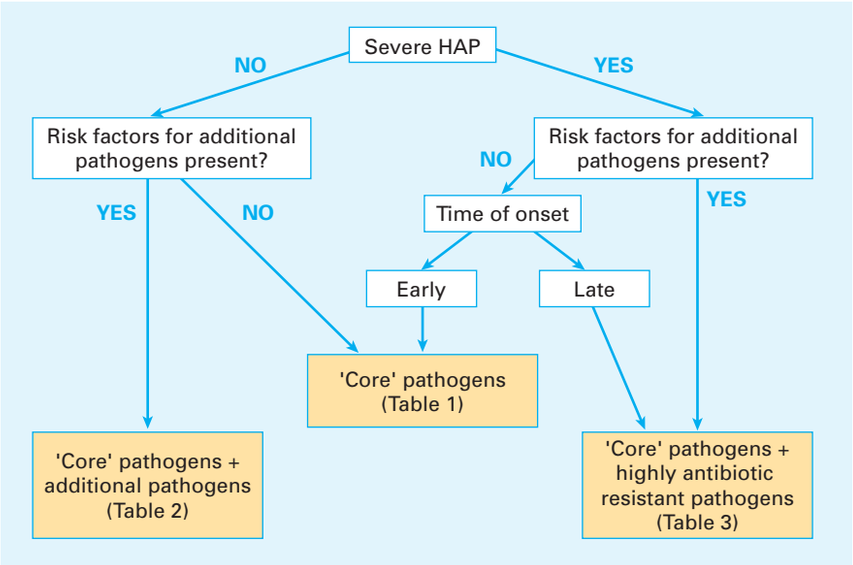

Fig 2. Classification of patients with hospital acquired pneumonia (HAP) (adapted from the American Thoracic Society consensus statement Fig 1[1]) (see Tables 1–3).

Pathogens involved

The potential pathogens associated with HAP are different from those associated with CAP and are influenced by three main factors (Fig 2)[1]:

1 Severity of illness.
2 Presence of risk factors for specific pathogens.
3 Time to onset of pneumonia.

Overall, enteric Gram-negative bacilli (eg Enterobacter spp, *Escherichia coli,* Klebsiella spp, Proteus spp and *Serratia marcescens*) and *S. aureus* are the main 'core' pathogens that must be considered in all cases (Table 1). Additional pathogens must be considered in specific situations (Table 2), including anaerobes, Legionella spp and resistant Gram-negative organisms such as *Pseudomonas aeruginosa.*

Methicillin-sensitive *S. aureus* is particularly associated with multiple trauma and comatose neurosurgical patients[11]. Fortunately, methicillin-resistant *S. aureus* is not common in these patients. In one ICU study, its acquisition was most strongly associated with previous antibiotic treatment for more than 48 hours[12]. An association with selective digestive decontamination regimens in the ICU has also been reported.

P. aeruginosa, the most common enteric Gram-negative bacilli isolated, is the leading cause of ventilator-associated pneumonia death, and is associated with prior antibiotic use, high-dose steroids, prolonged ICU stay and structural lung disease. Its importance in HAP increases with increasing disease severity (Table 3).

Anaerobic organisms can be identified in up to one-third of cases of HAP using invasive techniques and specific anaerobic cultures. However, their significance is unclear, particularly in patients who have not aspirated.

Table 1. Aetiology and management of non-severe hospital-acquired pneumonia (HAP) and early-onset severe HAP, with no additional risk factors.

'Core' organisms	Recommended antibiotics
Enteric Gram-negative bacilli:	
Enterobacter spp	2nd or 3rd generation cephalosporins
Escherichia coli	*or*
Klebsiella spp	beta-lactam/beta-lactamase inhibitor
Proteus spp	combination (eg co-amoxiclav)
Serratia marcescens	
Haemophilus influenzae	If penicillin allergic:
Streptococcus pneumoniae	fluoroquinolone or clindamycin + aztreonam
Methicillin-sensitive *Staphylococcus aureus*	

Adapted from the American Thoracic Society consensus statement, Table 1[1].

Table 2. Aetiology and management of non-severe hospital acquired pneumonia (HAP) with risk factors for additional pathogens present.

Risk factor	Possible pathogen (in addition to 'core' organisms)	Recommended antibiotics to cover additional pathogen (added to 'core' antibiotic)
Recent thoraco-abdominal surgery Impaired swallowing Witnessed aspiration Dental sepsis	Anaerobes	Clindamycin *or* beta-lactam/beta-lactamase inhibitor
Coma Head trauma Neurosurgery Diabetes mellitus Renal failure	*Staphylococcus aureus*	If MRSA possible, consider adding vancomycin
High-dose steroids Organism endemic in hospital	Legionella spp	Macrolide (eg erythromycin or clarithromycin) +/– rifampicin +/– fluoroquinolone
Prior antibiotics High-dose steroids Prolonged ICU stay Structural lung disease	*Pseudomonas aeruginosa*	Treat as severe HAP**

* see Table 1
** see Table 3
Adapted from the American Thoracic Society consensus statement, Table 2[1].
ICU = intensive care unit; MRSA = methacillin-resistant *Staphylococcus aureus*.

Clinical features

Fever, purulent sputum or tracheal secretions, leucocytosis and new pulmonary infiltrates on chest X-ray occurring 48 hours or more after hospital admission are the cardinal features of HAP. Unfortunately, while these clinical features may be useful in patients on general wards, they may lead to over- or under-diagnosis of HAP in patients on MV particularly in the presence of adult respiratory distress syndrome[13]. In one ICU study, microbiologically confirmed pneumonia was established in less than half the patients with a clinical diagnosis of pneumonia[14].

Definitions for 'definite' and 'probable' pneumonia were put forward at the International Consensus Conference in 1992[15] – a division which is not very helpful to the clinician. In practice, it is reasonable to consider patients on MV as at risk of HAP if they develop new lung infiltrates and have purulent tracheal aspirates. A definite diagnosis of HAP then depends on microbiological confirmation either by quantitative culture from protected specimen bronchial brush samples or by the presence of intracellular bacteria in cells from an adequate bronchoalveolar lavage cytospin.

The definition of severe HAP is less well developed than that of CAP. A working definition, based on the American Thoracic Society (ATS) guidelines and on definitions developed for CAP, is given in Table 4[1].

Table 3. Aetiology and management of severe hospital acquired pneumonia (HAP) (excluding early-onset HAP with no risk factors where only 'core' pathogens are likely).

Organisms in addition to 'core' pathogens	Recommended antibiotics
Pseudomonas aeruginosa Acinetobacter spp	Aminoglycoside or ciprofloxacin *plus one of*: • antipseudomonal beta-lactamase stable beta-lactam antibiotic • imipenem *or* • aztreonam*
MRSA (in some hospitals)	• *and* vancomycin, if MRSA possible

* not if Gram-positive or *Haemophilus influenzae* infection suspected.
Adapted from the American Thoracic Society consensus statement, Table 3[1].
MRSA = methacillin-resistant *Staphylococcus aureus*.

Investigations

General

Investigations helpful both in establishing a diagnosis and in assessing the severity of HAP include:

- full blood count
- urea and electrolytes
- liver function tests
- C-reactive protein
- chest X-ray
- assessment of oxygenation by pulse oximetry or arterial blood gases.

Microbiology

Blood cultures should always be taken. Positive blood cultures are obtained in 20% of patients with HAP and denote a worse prognosis[1]. Sources of bacteraemia other than the lung need to be considered. Pleural fluid should always be sampled to detect complicated parapneumonic effusions requiring drainage. Urine samples for the rapid detection of antigens to Legionella and *S. pneumoniae* may be useful.

Techniques for sampling the lower respiratory tract, which are constantly under development, are listed in Table 5[16]. The debate about the sensitivity and specificity of the different techniques is heightened by the lack of a clear 'gold standard' for the diagnosis of pneumonia. In all instances, prior antibiotic treatment adversely affects diagnostic rates. Invasive techniques may influence immediate management, but

Table 4. Definition of severe hospital acquired pneumonia.

General	Admission to ICU required
Chest radiograph	Multilobar, cavitating or rapidly progressing lung infiltrates
Respiratory failure	Need for mechanical ventilation Need for >35% oxygen to maintain arterial oxygen saturation >90%
Evidence of severe sepsis	Shock (systolic BP <90 mmHg or diastolic BP <60 mmHg) Need for inotropic support for >4 hours Urine output <29 ml/hour or <80 ml in 4 hours Renal dialysis required

Adapted from the American Thoracic Society consensus statement, Table 4[1].
BP = blood pressure; ICU = intensive care unit.

it is not clear whether they improve outcome. Such techniques are probably best performed only where clinical and laboratory expertise is available and results are applied to management decisions as part of an agreed management protocol.

Management

General principles

Underlying disease may be worsened by HAP, and hence additional therapy must be considered. Where the diagnosis is uncertain, empirical therapy directed at other diagnoses may also be necessary (eg anticoagulation for suspected pulmonary embolism). Attention to fluid balance, oxygen therapy and nutritional status is important and chest physiotherapy may be helpful.

Empirical antibiotic therapy

Guidelines from the ATS[1] and the Canadian Consensus Conference[17] have been published, and the recommendations of the former for empirical antibiotic therapy are summarised in Tables 1–3. As in CAP, assessment of disease severity is central. Patients with severe HAP usually require empirical combination antibiotic therapy to cover all likely pathogens. Those with non-severe HAP can usually be treated with single agent antibiotic therapy if no additional risk factors are present. However, the mortality from HAP remains high even with effective treatment.

Prevention

Strategies to prevent the development of HAP are important in view of its high costs and increased mortality[18]. The general principles of encouraging shorter hospital stays and operation times, together with minimal invasive procedures (including early removal of nasogastric and endotracheal tubes), apply to all patients. Good airway management for patients undergoing general anaesthesia and attention to swallowing in patients at risk of aspira-

Key Points

Hospital acquired pneumonia (HAP) adds 5–9 days to the hospital stay of survivors, and the crude mortality rate may be as high as 70%

Aspiration of bacteria that colonise the upper respiratory tract is the main route of infection. Avoidance of factors that promote colonisation (eg raising gastric pH) or aspiration (eg supine position, nasogastric tube placement) decrease the risk of HAP

Enteric Gram-negative bacilli (eg Enterobacter spp, *Escherichia coli*, Klebsiella spp, Proteus spp, *Serratia marcescens*) and *Staphylococcus aureus* are the most common pathogens identified and must be considered in all cases

Disease severity and time of onset of infection from hospital admission are major factors to consider when deciding on empirical antibiotic therapy

Table 5. Techniques for sampling the lower respiratory tract in patients with suspected hospital acquired pneumonia (reproduced, with permission, from Ref 16).

Technique		Special equipment required (bedside + lab)	Skill required	Risk of technique	Sensitivity	Specificity
Non-invasive techniques	Expectorated sputum	0	0/+	0	+	+
	Endotracheal aspirate	+	+	0/+	++	+
	Blind distal airways sampling	+++	++	+	++	++
Perbronchoscopic invasive procedures	Protected specimen brush	+++	+++	++	+++	++++
	Bronchoalveolar lavage	+++	+++	++	++++	+++
	Protected bronchoalveolar lavage	++++	++++	++	++++	++++
Non-bronchoscopic invasive procedures	Percutaneous lung needle aspirate	+	+++	+++	++	++++
	Transtracheal aspiration	+++	++++	+++	+++	++
	Pleural fluid sampling	+	++	+	+	++++
Open lung biopsy invasive procedures		++++	++++	+++	++++	++++

tion (eg those with impaired level of consciousness) are important. Patients admitted electively to hospital can contribute by maximising their level of fitness through weight reduction in the obese, cessation of smoking and optimal control of coexisting illnesses (eg diabetes mellitus). Specific measures mainly aimed at reducing colonisation are listed in Table 6.

Table 6. Specific measures to prevent the development of hospital acquired pneumonia (HAP).

Strategy	Comments
• Hand washing	Simple and effective means of reducing transfer of organisms[19] Frequently underperformed
• Selective digestive decontamination	Involves systematic use of topical antibiotics applied to the oropharynx and stomach and intravenous cefotaxime A meta-analysis of trials has shown this to reduce respiratory tract infections and mortality[20] Risk of promoting bacterial resistance[21] Enthusiasm for this measure varies
• Maintenance of low gastric pH	A meta-analysis has shown a trend towards increased risk of pneumonia in patients treated with H2-antagonists[22]. Based on this and other evidence, routine use of H2-antagonists and antacids as an anti-ulcer strategy is no longer recommended Sucralfate is seen as safer, although a recent RCT found it less effective at preventing gastrointestinal bleeding[23,24].
• Semi-recumbent position	Nursing the patient in the semi-recumbent position limits transfer of bacteria into the airways The supine position is associated with increased risk of HAP[25].

RCT = randomised controlled trial.

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